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CLINICAL TRIALS AND OBSERVATIONS

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Do CARs finally hit the CLL road?

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In this issue of *Blood*,[1] Siddiqi et al summarize their phase 1/2 dose-escalation chimeric antigen receptor T (CART) trial for patients with chronic lymphocytic leukemia (CLL), including those who had failed prior ibrutinib treatment. Twenty-five patients with ibrutinib refractory/relapsed CLL/small lymphocytic lymphoma, enriched for high-risk features (half of the patients had complex karyotype and more than half had TP53 aberrations), received anti-CD19 CART19 cells following lymphodepleting chemotherapy. The CART19 product, lisocabtagene, consists of 2 separate infusions of separately activated, transduced, and expanded autologous CD4$^+$ and CD8$^+$ cells. Although most patients had cytokine release syndrome (CRS), 90% experienced mild disease. Neurotoxicity occurred in 40%, with half of these high grade. Complete responses were observed in 10 patients. Nine of these also had undetectable MRD (uMRD), which was achieved early after infusion. A clear association was observed between uMRD and duration of response: just 3 months in patients with MRD$^+$ vs not reached in patients with uMRD. One-quarter of patients that progressed after CART19 cells had Richter transformation (RT). A follow-up phase study is currently underway.

The chimeric antigen receptor (CAR) construct used in this study is the FMC63-based anti-CD19 CAR19 that includes an immunoglobulin G4 hinge domain, CD28 transmembrane domain, and signals through CD3-ζ and 4-1BB. These signaling domains in other, slightly different CD19 CAR designs had induced durable remissions in CLL patients, but in a smaller proportion.[2] In the current report, lisocabtagene was evaluated in ibrutinib failures. The authors reveal that in the 22 efficacy-evaluable patients, lisocabtagene induced an overall response rate of 82% and complete remissions in 10 patients. These data therefore suggest that CART cells are efficacious in patients who fail next-generation small molecule treatments.

CART therapy is associated with specific potential life-threatening toxicities. Most common toxicities are hyperinflammatory based and include CRS and neurologic toxicity. In severe cases, immunosuppressive therapy is needed, which further worsens the already compromised immune systems of these patients, both because of the underlying disease and the lymphodepleting therapy. CART cell efficacy and bulky disease have been correlated with CRS severity and with the development of neurologic toxicity.[3] In the setting of CLL, it is hard to predict the magnitude of CAR-induced inflammation. On the one hand, the high tumor burden often present in CLL could provoke rapid inflammation following CART infusion, as has been described in acute lymphoblastic leukemia.[4] On the other hand, acquired T-cell dysfunction, a well-reported phenomenon in CLL,[5] has been associated with reduced CART cell responses in CLL.[6] Gauthier et al used the same CAR design as in the current study but started patients with CLL on ibrutinib just prior to apheresis collection, which led to less severe toxicities, possibly because of direct effects on the CART cells and indirect effects by altering CLL–T-cell interations.[7]

In this trial, a strong association was seen between MRD and clinical outcome. uMRD was reached in 15 out of 20 evaluable patients in blood and 13 evaluable patients in the marrow. Most patients achieving uMRD reached this level of disease clearance by day 30 postinfusion. These findings imply that efficacy of CART cells is highest early after infusion. This is in line with transcriptomic analyses in an earlier CART study in CLL that showed that the majority of CART cells had effector rather than memory functions with signs of exhaustion and apoptosis, implying impaired memory formation and lack of persistence of CART cells in patients with CLL.[6] Whether the association of MRD and outcome has also clinical relevance is much less clear. MRD might serve as an early surrogate marker for outcome, as it does for both chemoimmunotherapy and venetoclax-containing regimens,[8] but its use for clinical decision making in the context of CART is rather limited. This is important for future development. For example, can CART efficacy be improved by addition of targeted agents in case of suboptimal responses?

As expected from ibrutinib failures, the tumor population has a few skeletons in their closet. Five of 22 efficacy evaluable patients developed an RT. This begs the question whether this was a preexisting population selected by this highly efficacious therapy, as described previously by Fraietta et al,[6] or induced by the therapy? Three of these 5 patients developed RT after an initial response.

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With the caveat of low patient numbers, the fact that no baseline factors were found to be associated with RT occurrence might point to a therapy-related causative factor. It has been suggested that besides genomic aberrations, such as TP53 disruption, C-MYC activation, trisomy 12, and NOTCH1 mutation, microenvironment remodeling also leads to the development of RT. This is reflected by changes in the immune signature of CLL and surrounding tissue after RT, such as high programmed death-1 expression by tumor cells and increased programmed death ligand-1 expression in histiocytes and dendritic cells, and lower peripheral blood T-cell receptor clonality.[9] One could therefore speculate that the proinflammatory state evoked by CART cells might actually push such microenvironmental changes and therefore lead to an increased incidence of RT.

In the present study, median follow-up was 2 years. Seven patients have completed 24-month follow-up after liso-cel infusion and are still in response, and 2 patients had ongoing responses beyond month 18 at time of data cutoff. Such stable remissions outperform other CART trials, including the study where another 4-1BB, CD3z-based CAR was used.[6] Whether this is a function of follow-up time, that is, with longer follow-up these patients will experience a return of their leukemia, or is it a function of the CAR design, which has CD28 as its transmembrane domain, is at present unclear. Muller et al recently demonstrated that a similar CAR design interacted with endogenous CD28, which positively altered the signaling function.[10] One may hypothesize that this presents a second-generation CAR, whose function is predominantly affected by the CD3 and 4-1BB moieties, but with a contributing role for the CD28 domain. It is hoped that further follow-up and research will shed light on either possibility, but if the latter is indeed the case, it would imply an important step forward for implementation of CAR-T in CLL.

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Comment on Niewisch et al, page 1807

Telomere biology disorders: ends and (genetic) means

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In this issue of *Blood*, Niewisch et al[1] analyzed the clinical features and outcomes associated with different germline genotypes of telomere biology disorders (TBDs). This study highlights the presentation and clinical implications of TBDs across all ages.

Telomeres are the specialized structures at the ends of chromosomes composed of repetitive DNA sequences complexed with proteins to protect free DNA ends and maintain genomic stability. TBDs are variably characterized by bone marrow failure, cancer predisposition, and multiorgan system complications, particularly liver fibrosis or cirrhosis and pulmonary fibrosis. Although the availability of genetic testing and telomere length testing has rapidly advanced the diagnosis of TBDs,[2] the variable phenotypes of TBDs pose significant challenges to prospective medical management. The development of evidence-based strategies for tailored clinical care is challenging for rare diseases. One standard approach for risk stratification is to analyze clinical outcomes based on the causative gene; however, certain TBD genes may cause disease with either heterozygous or biallelic mutations. To account for this allelic complexity, this study analyzed outcomes over time for 200 patients based on both genotype and inheritance pattern: recessive (*DKC1*, 32; *RTEL1*, 15; *CTC1*, 6; *PARN*, 4; *WRAP53*, 3; *TERT*, 2; *ACD*, 2), dominant/heterozygous

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